IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Applicants	:	Jayati Ghosh et al.
Application No.	:	10/763,645
Filed	:	January 22, 2004
For	:	Classification of pixels in a microarray image based on pixel intensities and a preview mode facilitated by pixel-intensity-based pixel classification

Examiner	:	ABDI, Amara
Art Unit	:	2609
Docket No.	:	10030722-1
Date	:	April 13, 2009

APPEAL BRIEF

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Sir:

This appeal is from the decision of the Examiner, in an Office Action mailed January 13, 2009, finally rejecting claims 1-9, 11, and 14-20.

REAL PARTY IN INTEREST

Agilent Technologies is the Assignee of the present patent application. Agilent Technologies, Inc., is a Delaware corporation with headquarters in Santa Clara, CA.

RELATED APPEALS AND INTERFERENCES

Applicant's representative has not identified, and does not know of, any other appeals of interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-9, 11, and 14-20 are pending in the application. Claims 1-9, 11, and 14-20 were finally rejected in the Office Action dated May 2, 2008. Claims 10, 12-13 are cancelled. Applicants' appeal the final rejection of claims 1-9, 11 and 14-20 which are copied in the attached CLAIMS APPENDIX.

STATUS OF AMENDMENTS

No Amendment After Final is enclosed with this brief. The last Amendment was filed February 2, 2008.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1

Claim 1 is directed to a method for classifying pixels of a microarray image (Figures 8A-E) with observed intensities within a region of interest, the method comprising: (1) initially classifying pixels in the region of interest (1002 in Figure 10) as either feature pixels (1302) or background pixels (1204) based on the intensities of the pixels (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9); and (2) iteratively computing (line 15 page 19 to line 26 of page 21), for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels (Figure 14).

Dependent Claims 2-9 and 11

Claim 2 is directed to the method of claim 1 wherein a feature-pixel and background-pixel classification is stored in a feature mask (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9). Claim 3 is directed to the method of claim 2 wherein the feature mask includes binary values corresponding to pixels in the region of interest (1002 in Figure 10), a first binary value indicating that a corresponding pixel is a feature pixel and a second binary value indicating that a corresponding pixel is a background pixel. Claim 4 is directed to the method of claim 1 wherein classifying pixels in the region of interest (1002 in Figure 10) as either feature pixels or background pixels based on the observed intensities of the pixels further includes (1102 in Figure 11; lines 10 of page 16 to

line 14 of page 19 and Figure 9): (1) determining a high pixel intensity and a low pixel intensity for the region of interest; (2) determining an intermediate point between the high pixel intensity and a low pixel intensity; (3) classifying pixels with observed pixel intensities greater than or equal to the intermediate point as feature pixels and classifying pixels with observed pixel intensities less than the intermediate point as background pixels; and (4) iteratively reclassifying pixels based on an intermediate intensity between the mean intensity of feature pixels and the mean intensity of background pixels. Claim 5 is directed to the method of claim 1 further including (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9) identifying hole pixels that are feature pixels surrounded by background pixels and background pixels surrounded by feature pixels and reclassifying hole pixels in order to increase continuity of feature-pixel and background-pixel classification with respect to location within the region of interest (1002 in Figure 10). Claim 6 is directed to the method of claim 1 wherein iteratively computing (line 15 page 19 to line 26 of page 21), for pixels within the region of interest (1002 in Figure 10), probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels further includes: iteratively (1) computing intensity-based outlier feature-pixel statistics and outlier background-pixel statistics; and (2) from the most recently computed intensity-based feature-pixel statistics and background-pixel statistics, determining, for each pixel, a Bayesian posterior probability $P(F/i,x)$ that the pixel is a feature pixel and a Bayesian posterior probability $P(B/i,x)$ that the pixel is a background pixel and classifying the pixel as a feature pixel when $P(F/i,x) >= P(B/i,x)$ until either a maximum number of iterations are performed or until fewer than a threshold number of pixels are reclassified from feature-pixel to background-pixel and from background-pixel to feature-pixel status in the most recently executed iteration. Claim 7 is directed to the method of claim 6 wherein the Bayesian posterior probability $P(F/i,x)$ is calculated as

$$P(F/i,x) = \frac{P(F,i,x)}{P(i,x)} = \frac{P(i/x,F)P(F,x)}{P(i,x)} = \frac{P(i/x,F)P(F/x)P(x)}{P(i,x)}$$

wherein the Bayesian posterior probability $P(B/i,x)$ is calculated as

$$P(B/i,x) = \frac{P(B,i,x)}{P(i,x)} = \frac{P(i/x,B)P(B,x)}{P(i,x)} = \frac{P(i/x,B)P(B/x)P(x)}{P(i,x)};$$

and wherein a pixel is classified as a feature pixel when

$\dfrac{P(F/i,x)}{P(B/i,x)} >= 1$ (line 15 page 19 to line 26 of page 21). Claim 8 is directed to the method of

claim 7 wherein Bayesian posterior probabilities P(F/i,x) and P(B/i,x) are calculated for each channel of a two-channel microarray (line 15 page 19 to line 26 of page 21), and a joint probability distribution function for two channels is then computed, which is then used for classifying pixels as feature pixels or background pixels. Claim 9 is directed to the computer-readable medium encoded with computer-executable instructions that implement the method of claim 1. Claim 11 is directed to the computer-readable medium encoded with computer-executable instructions that implement a feature extraction program (Figures 18 and 19; line 14 of page 23 to line 23 of page 24) that includes a feature-location-and-size determination step that includes the method for classifying pixels with observed intensities within the region of interest of claim 1.

Independent Claim 14

Claim 14 is directed to a feature-extraction system (Figures 18 and 19; line 14 of page 23 to line 23 of page 24) comprising: (1) a means for receiving and storing a scanned image of a microarray (Figures 8A-E; lines 16-18 of page 23)); (2) a gridding means (lines 17-18 of page 23) for determining putative feature positions and sizes within the scanned image of the microarray; (3) feature-mask-generating logic (lines 10 of page 16 to line 14 of page 19 and Figure 9) that classifies pixels as feature-pixels and background-pixels based on pixel locations and intensities; (4) preview-mode display logic (lines 6-8 of page 24) that displays feature positions and sizes obtained from the generated feature mask, solicits feedback from a user, and corrects the feature positions and sizes; and (5) a feature extraction module (lines 1-22 of page 24) that extracts signal data from the scanned image of the microarray following user acceptance of initial feature locations and sizes displayed in preview mode.

Dependent Claims 15-20

Claim 15 is directed to the feature-extraction system of claim 14 wherein the feature-mask-generating logic (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9) classifies pixels as feature-pixels and background-pixels based on pixel locations and intensities by: (1) initially classifying pixels in a region of interest (1002 in Figure 10) as either feature pixels or background pixels based on the intensities of the pixels;

and (2) iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels. Claim 16 is directed to the feature-extraction system of claim 15 wherein a feature-pixel and background-pixel classification is stored in a feature mask (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9). Claim 17 is directed to the feature-extraction system of claim 15 wherein classifying pixels in the region of interest (1002 in Figure 10) as either feature pixels or background pixels based on the observed intensities of the pixels further includes (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9): (1) determining a high pixel intensity and a low pixel intensity for the region of interest; (2) determining an intermediate point between the high pixel intensity and a low pixel intensity; (3) classifying pixels with observed pixel intensities greater than or equal to the intermediate point as feature pixels and classifying pixels with observed pixel intensities less than the intermediate point as background pixels; and (4) iteratively reclassifying pixels based on an intermediate intensity between the mean intensity of feature pixels and the mean intensity of background pixels. Claim 18 is directed to the feature-extraction system of claim 15 wherein iteratively computing (line 15 page 19 to line 26 of page 21), for pixels within the region of interest (1002 in Figure 10), probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels further includes: iteratively (1) computing intensity-based outlier feature-pixel statistics and outlier background-pixel statistics; and (2) from the most recently computed intensity-based feature-pixel statistics and background-pixel statistics, determining, for each pixel, a Bayesian posterior probability $P(F/i,x)$ that the pixel is a feature pixel and a Bayesian posterior probability $P(B/i,x)$ that the pixel is a background pixel and classifying the pixel as a feature pixel when $P(F/i,x) >= P(B/i,x)$; until either a maximum number of iterations are performed or until fewer than a threshold number of pixels are reclassified from feature-pixel to background-pixel and from background-pixel to feature-pixel status in the most recently executed iteration. Claim 19 is directed to the feature-extraction system of claim 18 wherein the Bayesian posterior probability $P(F/i,x)$ is calculated as

$$P(F/i,x) = \frac{P(F,i,x)}{P(i,x)} = \frac{P(i/x,F)P(F,x)}{P(i,x)} = \frac{P(i/x,F)P(F/x)P(x)}{P(i,x)} ;$$

wherein the Bayesian posterior probability $P(B/i,x)$ is calculated as

$$P(B/i,x) = \frac{P(B,i,x)}{P(i,x)} = \frac{P(i/x,B)P(B,x)}{P(i,x)} = \frac{P(i/x,B)P(B/x)P(x)}{P(i,x)};$$

and wherein a pixel is classified as a feature pixel when

(line 15 page 19 to line 26 of page 21) $\frac{P(F/i,x)}{P(B/i,x)} >= 1$. Claim 20 is directed to the feature-extraction system of claim 19 wherein Bayesian posterior probabilities P(F/i,x) and P(B/i,x) are calculated for each channel of a two-channel microarray, and a joint probability distribution function for two channels is then computed, which is then used for classifying pixels as feature pixels or background pixels (line 15 page 19 to line 26 of page 21).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1.   The rejection of claims 1-4, 9, and 11 under 35 U.S.C. §102(b) as being anticipated by Yakhini et al., EP 1 162 572 A2.

2.   The rejection of claim 5 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., EP 1 162 572 A2 in view of Lee et al., U.S. Patent Application Publication No. 2004/0202368.

3.   The rejection of claims 6-7 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., EP 1 162 572 A2 in view of Bow et al., STIC.

4.   The rejection of claim 8 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al. and Bow et al., STIC, in further view of Padilla et al., U.S. Patent Application Publication No. 2003/0233197.

5.   The rejection of claims 14-17 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., EP 1 162 572 A2 in view of Shams, U.S. Patent No. 6,990,221.

6.   The rejection of claims 18 and 19 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., EP 1 162 572 A2 and Shams, U.S. Patent No. 6,990,221 in further view of Bow et al., STIC.

7.   The rejection of claim 20 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., Shams, U.S. Patent No. 6,990,221, and Bow et al., STIC, in further view of Padilla et al., U.S. Patent Application Publication No. 2003/0233197.

ARGUMENT

The current claims were finally rejected in an office action dated May 2, 2008. In that office action, Yakhini et al., EP 1 162 572 A2 ("Yakhini"), was used as a primary reference. In response to that final rejection, Appellants filed an appeal brief on October 2, 2008. In response to the filed appeal brief, the Examiner has apparently re-opened prosecution in an office action dated January 13, 2009 ("Office Action"), stating on page 2: "Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn." Appellants' representative does not find a "request for reconsideration of the finality of the rejection of the last Office action" in the originally filed appeal brief. Although the Examiner does not explicitly state what the current status of the current application is, Appellants assume that the Examiner has re-opened prosecution. On page 2 of the Office Action, the Examiner states: "Applicant's arguments with respect to claims 1-11, and 14-20 have been considered but are moot in view of the new ground(s) of rejection." While the Examiner's specific rejections have somewhat changed, the rejections are nonetheless primarily based on Yakhini, which, as discussed in the originally filed appeal brief, does not teach, mention, or suggest the current invention. In the Office Action, the Examiner rejects claims 1-4, 9, and 11 under 35 U.S.C. §102(b) as being anticipated by Yakhini, rejects claim 5 as being unpatentable under 35 U.S.C. §103(a) over Yakhini in view of Lee et al., U.S. Patent Application Publication No. 2004/0202368 ("Lee"), rejects claims 6-7 under 35 U.S.C. §103(a) as being unpatentable over Yakhini in view of Bow et al., STIC ("Bow"), rejects claim 8 under 35 U.S.C. §103(a) as being unpatentable over Yakhini and Bow in further view of Padilla et al., U.S. Patent Application Publication No. 2003/0233197 ("Padilla"), rejects claims 14-17 under 35 U.S.C. §103(a) as being unpatentable over Yakhini in view of Shams, U.S. Patent No. 6,990,221 ("Shams"), rejects claims 18 and 19 under 35 U.S.C. §103(a) as being unpatentable over Yakhini and Shams in further view of Bow, and rejects claim 20 under 35 U.S.C. §103(a) as being unpatentable over Yakhini, Shams, Bow, and further in

view of Padilla. Appellants respectfully traverse all of the 35 U.S.C. §102(b) and 35 U.S.C. §103(a) rejections.

ISSUE 1

1.   The rejection of claims 1-4, 9, and 11 under 35 U.S.C. §102(b) as being anticipated by Yakhini et al., EP 1 162 572 A2.

As discussed in the first sentence of the background-of-the-invention section of the current application, beginning on line 11 of page 1: "The present invention is related to methods and systems for determining which pixels, in a digital image of a microarray, are associated with features of the microarray, and which pixels are background pixels associated with inter-feature regions of a microarray." The current application provides a very lengthy and detailed discussion of microarrays, microarray features, background pixels, and inter-feature regions. This discussion begins on line 19 of page 1 and continues to line 30 of page 6, and then resumes on line 11 of page 9 and continues through line 22 of page 15. A microarray is a manufactured product that comprises a substrate onto which features are arranged in a regular two-dimensional grid or lattice. Each feature contains a different type of probe molecule, generally oligonucleotides. Figures 4-7 of the current application illustrate the general concept of a microarray.

Microarrays are scanned, by microarray scanners, to produce digitally encoded images of the surface of the microarray. Target molecules bound to probe molecules of different features emit light or other types of radiation that can be imaged to produce raw data, such as a portion of a microarray image shown in Figure 8A of the current application. Figure 8A of the current application, as discussed in the current application beginning on line 31 of page 13, shows a 25 x 25 pixel region of a digital image of a microarray. "Each two-digit number in the two-dimensional array of numbers in Figure 8A, such as the two-digit number '02' 802, represents the intensity associated with the pixel." Figure 8B of the current application shows the approximately elliptical line boundaries of two elliptical-disk-like regions within the portion of the microarray image shown in Figure 8B. These elliptical line boundaries can be thought of as contour lines, such as the contour lines on a topographical map, which show the boundaries between regions with different average intensities. Outside of the larger, disk-shaped region bounded by roughly elliptical line 812, referred to in Figure

8B as region 814, pixel intensities are relatively low, with an average intensity value, by inspection, somewhere between 8 and 11. The region bounded by the roughly elliptical line 810 and the roughly elliptical line 812 is an intermediate-intensity region in which pixel intensities have an average value, by inspection, of somewhere between 2400 and 2500 (note the two-digit numbers in Figures 8A-E refer to 100's of counts, or other signal-intensity units). The innermost region, bounded by the roughly elliptical line 810, contains pixels having high-intensity values with an average value, by inspection, of between 4900 and 5000. These regions, shown in Figure 8B, comprise an ideal image of a single feature of a microarray. The region outside of the roughly elliptical line 812, referred to as 814 in Figure 8B, constitutes a background region, or an inter-feature region.

In many cases, the signals produced by microarray features and image of a microarray are not so well differentiated from background, so that it is difficult to determine which portion of the image corresponds to background and which portion corresponds to a region of interest corresponding to a microarray feature. Figures 8C-E illustrate portions of microarray images encompassing a feature that cannot be so easily visually distinguished as in the case of Figures 8A-B. As discussed beginning on line 21 of page 16 of the current application, Figure 10 shows a portion of a microarray image clearly containing the image of a feature 1004, but also containing two other relatively high-intensity regions 1008 and 1010. As discussed in the current application beginning on line 31 of page 16:

> It is a goal of feature-mask generation to accurately identify those pixels within the pixel-based ROI intensity data set that correspond to the image of a feature and to mask out high-intensity pixels, such as those in regions 1008 and 1010 in Figure 10, that do not correspond to feature pixels. In addition, there may be various, isolated intensity-outlying pixels, both in the background and feature regions of an ROI, that also need to be identified and taken into consideration during signal extraction from pixel-intensity data.

The approach to distinguishing feature pixels from background pixels within a region of interest is described in the current application beginning on line 23 of page 15, with reference to Figures 9-19. A preliminary feature mask, shown in Figure 11, is generated from the region of interest by partitioning pixels of the region of interest between candidate feature pixels, represented by Boolean value "1," and candidate background pixels, represented by Boolean value "0." Note that the three high-intensity regions discussed with reference to Figure 10 appear in Figure 11 as regions largely containing Boolean value "1." Employing various operations, a final feature mask, shown in Figure 14, is produced in which the feature

pixels are identified by Boolean value "1" and the non-feature, background pixels are identified by Boolean value "0." Details of the methods by which this final feature mask are generated can be found in the detailed description of the current application.

The Yakhini reference is related to processing of microarray data. In fact, Appellants' representative drafted both Yakhini as well as the current application. Yakhini is not directed, however, to the subject matter to which the current application and current claims are directed, namely, classifying pixels within the region of interest of a microarray image as background pixels or feature pixels, but is instead directed to constructing and orienting a two-dimensional rectilinear grid that is superimposed over the image of a microarray in order to identify and index the features within the microarray image.

Claim 1 of the current claim set, as one example, includes a step of initially classifying pixels as feature pixels or background pixels based on pixel intensities, and a second step of iteratively computing probabilities that pixels are feature pixels and probabilities that pixels are background pixels based on the locations and intensities of the pixels in order to classify pixels as feature pixels or background pixels.

The Examiner's arguments with respect to Yakhini, beginning on page 2 of the Office Action and extending to the middle of page 3, make little sense. First, the Examiner cites lines 1-2 of paragraph [0015] apparently for the proposition that Yakhini teaches a method and computer program. Indeed, Yakhini does teach a method and computer program. However, the method and computer program taught by Yakhini is quite different from, and not related to, the method of claim 1 of the current application.

Next, the Examiner cites Figure 5 and paragraph [0022] on page 6 and Figures 31 and 32, and paragraph [0067] of Yakhini as teaching "classifying pixels of a microarray image with observed intensities within a region of interest. Paragraph [0022] is concerned with calculation of a portion of a column vector corresponding to a single region of a microarray image. The column vector 504 in Figure 5 is shown below a square portion of a microarray image including a feature. There is no mention in paragraph [0022] or in Figure 5 of classification of pixels. The column vector is obtained by summing the intensities within the columns of the square portion of the microarray image, essentially projecting a two-dimensional portion of the intensity data in the image into a one-dimensional vector. Figure 5 and paragraph [0022] are unrelated to the current disclosure and to the currently claimed invention.

Figures 31 and 32 do show a portion of an image of a microarray partitioned

into cells, each cell containing a disk-shaped feature region surrounded by an annular region. Annular regions surrounding the central disk are referred to as "local backgrounds" in paragraph [0067] and the disk-shaped regions are referred to as "features." The phrase "region of interest" does not occur in paragraph [0067], nor does paragraph [0067] teach, mention, or suggest how the local backgrounds and features are determined. Paragraph [0067] is concerned with, as explicitly stated in paragraph [0067], determining a general microarray-image background level to subtract from each feature signal. It is in no way concerned with determining the shapes, boundaries, or locations of the annular local-background regions, disk-shaped feature regions within the two-dimensional grid shown in Figures 31 and 32. To those familiar with scientific data processing and data analysis, it is readily apparent, from casual observation of Figures 31 and 32, that the feature regions and the annular local-background regions are all of identical size and geometry, and are all positioned with centers exactly corresponding to the centers of the cells of the two-dimensional grid which contain them. Those familiar with science and with data analysis will immediately recognize that the size, shape, and location of the feature disks and annular local backgrounds appear not to be determined from the local data of the cells in which they are positioned, but are instead assigned according to a common algorithm based on the parameters which characterize the two-dimensional grid. Indeed, in the third sentence of paragraph [0039], Yakhini describes the algorithm for determining the outer boundary of the annular local-background region: "The outer region of interest is the maximally-sized elliptical area that will fit within the rectangular portion of a scanned image overlying and centered on a particular feature." Computation of the boundary of the disk-shaped feature region, such as the disk-shaped feature regions 3112-3120 shown in Figure 31, is, like calculation of the outer-region-of-interest boundary, not taught, mentioned, or suggested in paragraph [0067] of Yakhini. Computation of the boundary of the disk-shaped feature region is discussed, in Yakhini, in paragraph [0038] beginning on page 8 and extending to page 9, with reference to Figure 16. As discussed in this paragraph, the feature boundary is determined as the "elliptical area 1602 having a minimum size that totally encompasses the feature" which is "centered within the area of the scanned image of the feature shown in Figure 16."

Thus, as repeatedly noted by Appellants' representative in both the originally filed appeal brief and in a previously filed response, Yakhini is not concerned with determining a classification of individual pixels in a region of interest as feature or

background pixels. Instead, Yakhini essentially centers a local-background annulus and a disk-shaped feature region within each cell of a two-dimensional grid. Yakhini clearly states that Yakhini is instead concerned with establishing a coordinate system corresponding to the two-dimensional rectilinear grid shown in Figures 31 and 32. In order to establish this grid, including the orientation of the vertical and horizontal grid lines, Yakhini does refine the coordinate system "to best correspond to the determined positions of the strong features" in the image of the microarray (See Summary of the Invention of Yakhini). But Yakhini does not in any way teach, mention, or suggest iteratively computing probabilities that features are feature pixels or background pixels. Instead, in determining the orientation of the rectilinear grid, Yakhini uses standard, geometrical shapes that are fit to, and determined by, the rectilinear grid to describe the local-background annulus and the feature disk of each cell.

Next, the Examiner again cites Figures 31 and 32, in paragraph [0067], of Yakhini as teaching "initially classifying pixels in the region of interest as either feature pixels or background pixels" and cites Figures 2 and 5, and paragraphs [0004] and [0022], as teaching that the initial classification is based on the intensities of the pixels. As discussed above, the classification expressed as the outer-region-of-interest annulus and the disk-shaped central feature are determined from a rectilinear two-dimensional grid that is fit to the microarray image, and are not determined by the intensities of the pixels within the region of interest. Paragraph [0067] does not teach, mention, or even remotely suggest a method for classifying individual pixels within a region of interest as background or feature pixels based on probabilities computed for the individual pixels. Paragraph [0022], as discussed above, is entirely unrelated to classification of pixels as being feature pixels or background pixels, instead discussing a method for computing a vector from a square region of a microarray image. Paragraph [0004] of Yakhini has been discussed repeatedly in a previously filed response and in the originally filed appeal brief. There is no mention or even remote suggestion in this paragraph for any method for which pixels in a region are classified as feature pixels or background pixels. The paragraph does discuss feature pixels and background pixels, but provides no indication on how a given pixel may be classified as feature or background, other than indicating that, in general, feature pixels inhabit a roughly disk-shaped region within a portion of a microarray image. This fact is assumed in the current application, as discussed beginning on line 14 of page 14 with reference to Figures 8A-B.

As stated in the current application, in the paragraph that begins on line 14 of

page 14: "As described above, currently employed techniques computationally identify an intensity moment, or centroid, in the subregion and then identify a feature region approximately coincident with the centroid based on intensity thresholding." The currently claimed invention and current disclosure are not directed to restating or reclaiming these currently employed techniques. Instead, the currently claimed and currently disclosed invention is discussed beginning on line 23 of page 15 of the current application, with reference to Figures 8-9, 15, 17, and 18. As explicitly claimed in the first two words of the second element of claim 1, the currently claimed method iteratively computes pixel classifications. The word "iterative" means a method that repeats a sequence of steps until a stopping point is reached. In step 912 of Figure 9, a routine labeled "iteratively refined mask" is called. This routine is the iterative step to which the first two words of the second element of claim 1 refer. Figure 15 of the current application provides a control-flow diagram for this iterative step. A series of routine calls (1502, 1504, 1506, 1508, and 1510) are made prior to testing, in step 1512, whether or not the iterative procedure has converged. If so, then the iterative procedure returns, in step 1514. Otherwise, as expressed by the arrow containing the word "NO," the sequence of routine calls are again made prior to again testing for convergence. There is no such iterative method for classifying pixels as being background pixels or feature pixels within a region of interest taught, mentioned, or even remotely suggested in Yakhini.

The Examiner fails to cite anything in Yakhini for teaching an iterative computing method. For this reason, alone, the Examiner's 35 U.S.C. §102(b) anticipation rejection must certainly fail. For a proper anticipation rejection, a single reference must teach or disclose all claim elements. It would appear that the Examiner has completely failed to appreciate the meaning of the phrase "iteratively computing."

For the term "probabilities" in the second element of claim 1, the Examiner cites paragraphs [0068], [0069], and [0070] of Yakhini. Anticipation rejections are based on finding teaching of inventions, and not on occurrence of particular terms and phrases used in a claim in a reference. Indeed, probabilities are discussed in these three paragraphs, but the probabilities have nothing to do with classification of individual pixels within a region of interest as being feature pixels or background pixels. Instead, Yakhini discusses, in general terms, various statistical metrics that can be used to estimate the collective background intensity for a microarray image. The term "probability" is a very general and widely applied term in science and mathematics. The fact that a probability may be used for characterizing

one aspect of a microarray image has nothing whatsoever to do with the fact that a different probability is computed for classifying pixels within a particular region of interest as being feature pixels or background pixels. The Examiner appears to conclude, in a parenthetical statement following the phrase "that the pixels are feature pixels" from the second element of claim 1, that feature pixels are pixels with lowest intensity. This is an entirely incorrect conclusion. The current application provides detailed and complete background information with regard to criteria for considering pixels to be feature pixels or background pixels. Whether or a not a pixel is a feature pixel or a background pixel is not necessarily based on the intensity of that pixel, but has to do with a distribution of pixel intensities across a region of interest, microarray manufacture, scanner characteristics, and other factors. As clearly stated in the current application on lines 14 and 15 of page 15: "Note that it is quite difficult to distinguish feature pixels from background pixels based on intensity alone." The paragraph goes on to state:

> Note also that these hypothetical examples are, in many ways, best-case types of examples, in that the feature region is regularly shaped and relatively uniform in intensity. In actual microarray data, features may be asymmetrical, may contain highly non-uniform intensities due to a large number of different possible procedural, experimental, and instrumental errors and instabilities, and may be substantially offset from their expected positions within the general grid-like, regular pattern in which features are deposited. All of these effects can lead to difficulties in employing the currently used, intensity-based feature-pixel/background-pixel partitioning methods described above.

Thus the Examiner's apparent assumption that feature pixels have lowest intensity is quite incorrect, and would appear to reveal that the Examiner has failed to understand either Yakhini or the current application. For much microarray data, it is, in fact, quite the opposite. Feature pixels often have higher intensities than background pixels, at least for those features from which a positive signal is obtained during microarray scanning.

At this point, the Examiner's rejection becomes, in Appellants' representative's respectfully offered opinion, confused. The Examiner continues to refer to paragraphs of Yakhini, discussed above, that have nothing to do with the currently claimed invention or current application. Paragraphs [0068], [0069], and [0070] of Yakhini discuss statistics used for various algorithms that, together, allow Yakhini to properly orient and construct a rectilinear grid that partitions a microarray image into features. These statistics have nothing whatsoever to do with classifying pixels within a region of interest as feature pixels or background pixels. Paragraphs [0004] and [0022] do not in any way concern classifying

pixels within a region of interest as background pixels or feature pixels. In fact, paragraph [0004] refers to the problems addressed in the current application by the currently claimed method. In this paragraph, Yakhini notes that, on lines 46-48, that pixels within a disk-shaped image of a feature may have zero intensity values or values outside the range expected for a feature due to various noise, instrumental, and experimental problems, and that, on lines 41-45, background pixels may have non-zero intensity values arising from a variety of different experimental and instrumental problems and noise. Yakhini concludes: "Thus, scanned images of molecular array features may often show noise and variation and may depart significantly from the idealized scanned image shown in Figure 1." This is exactly what the current application states in the paragraphs preceding the discussion of the currently claimed invention, beginning on line 23 of page 15, as discussed above. Again, Yakhini does not endeavor to address these problems, and provides no method for attempting to classify pixels within a region of interest as background pixels or feature pixels based on the locations and intensities of the pixels. As discussed above, Yakhini simply assumes elliptical shapes for local backgrounds and feature disks and centers these shapes within a cell of a rectilinear grid. Yakhini is concerned in optimizing the construction of the rectilinear grid and orienting the rectilinear grid, and not, in any way, with classifying pixels within regions of interest as feature pixels or background pixels. Paragraph [0022] is, as discussed above, entirely and completely unrelated to the currently claimed invention, discussing computation of a column vector and adding the intensities in columns of pixels within a region of a microarray image.

Again, to emphasize the differences between the disclosures of Yakhini and the current application, Yakhini is directed to computing a rectilinear grid and orienting the rectilinear grid, in optimal fashion, to partition a microarray image into rectangular regions that each include a single feature. This is an initial step in the analysis of a scanned microarray image. Yakhini assumes an elliptical outer boundary for a local background and assumes a disk-shaped feature region within each cell of the rectilinear grid, the shape, position, and size of both the outer background annulus and feature disk geometrically determined by the rectilinear grid. Yakhini does employ various masking operations, blob analysis, and other such operations in which intensities of pixels are considered, but does so only in order to define the rectilinear grid. Yakhini is simply not concerned with classifying pixels within each cell of the rectilinear grid as feature pixels or background pixels based on the intensities and locations of the pixels within the cell.

By contrast, the current application addresses the problems referenced by Yakhini in paragraph [0004] and described in the background-of-the-invention section of the current application up to line 15 of page 15. Because it is difficult to determine which pixels are feature pixels and which pixels are background pixels from intensity alone, the currently claimed method makes an initial classification of the pixels within a region of interest and then iteratively computes probabilities, for each pixel, that the pixel is a feature pixel or a background pixel. Following this iterative step, pixels are classified as feature pixels or background pixels based on the iteratively computed probabilities. Again, to re-emphasize the differences between the current application and Yakhini, Yakhini assumes that the sizes and locations of the elliptical local-background annuli and disk-shaped features are determined by a rectilinear grid fit to a microarray image, and does not determine background and feature regions within a region of interest by initially assigning the pixels as background or feature pixels and then iteratively computing probabilities that each pixel is a background pixel or feature pixel. There is no teaching, mention, or suggestion in Yakhini for any kind of iterative pixel-classification method.

2.   The rejection of claim 5 under 35 U.S.C. §103(a) as being unpatentable over Yakhini in view of Lee.

In rejecting claim 5 under 35 U.S.C. §103(a), the Examiner relies primarily on Yakhini. However, as discussed in the section related to the first issue, Yakhini does not teach, mention, or even remotely suggest the currently claimed invention. Therefore, the 35 U.S.C. §103(a) rejection of claim 5 must certainly fail. Moreover, Lee in entirely unrelated to the current application. Lee is concerned with generalized learning programs that segment images. Lee does not teach, mention, or suggestion anything at all related to microarray-image analysis.

3.   The rejection of claims 6-7 under 35 U.S.C. §103(a) as being unpatentable over Yakhini in view of Bow.

In rejecting claims 6-7 under 35 U.S.C. §103(a), the Examiner relies primarily on Yakhini. However, as discussed in the section related to the first issue, Yakhini does not teach, mention, or even remotely suggest the currently claimed invention. Therefore, the 35

U.S.C. §103(a) rejection of claims 6-7 must certainly fail. Moreover, the Examiner appears to have cited Bow simply because equation 5.9 uses notation similar to that used in the expression $P(F/i,x) \geq P(B/i,x)$. Were the Examiner to read the text accompanying equation 5.9 in Bow, the Examiner would discover that this equation does not stand for anything at all related to the expression $P(F/i,x) \geq P(B/i,x)$. For one thing, the expression $P(F/i,x) \geq P(B/i,x)$ includes the relational operator ">=", while equation 5.9 does not. The meaning of these symbols is explained in many elementary mathematics textbooks. For another, as those familiar with mathematics well understand, one cannot simply arbitrarily replace symbols in one expression with symbols from another and end up with an expression that is correct, or has any meaning whatsoever. Finally, the claims clearly spell out what the expression $P(F/i,x) \geq P(B/i,x)$ means: a Bayesian posterior probability $P(F/i,x)$ that the pixel is a feature pixel and a Bayesian posterior probability $P(B/i,x)$ that the pixel is a background pixel and classifying the pixel as a feature pixel when $P(F/i,x) \geq P(B/i,x)$. There is nothing relevant to this expression in equation 5.9.

4.   The rejection of claim 8 under 35 U.S.C. §103(a) as being unpatentable over Yakhini and Bow in further view of Padilla.

In rejecting claim 8 under 35 U.S.C. §103(a), the Examiner relies primarily on Yakhini. However, as discussed in the section related to the first issue, Yakhini does not teach, mention, or even remotely suggest the currently claimed invention. Therefore, the 35 U.S.C. §103(a) rejection of claim 8 must certainly fail. Moreover, Padilla is entirely and completely unrelated to the current application or current claims. The Examiner appears to cite Padilla merely because Padilla mentions a microarray analysis and Bayesian analysis. Apparently, the Examiner is unaware that Bayesian analysis a very large field in mathematics, with thousands of different applications. Padilla does not, in any way, teach, suggest, or even remotely touch on assigning probabilities to pixels within a region or interest as being background or feature pixels - whether by Bayesian methods or by any other. The coincidence of terms in a reference is not sufficient grounds for asserting that the reference has anything to do with an application or claims, let alone form the basis of an obviousness-type rejection. Both obviousness and anticipation analysis are concerned with comparing a claimed invention with a teaching or suggestion in one or more references, not with coincidentally finding a few claim terms in the reference.

5.   The rejection of claims 14-17 under 35 U.S.C. §103(a) as being unpatentable over Yakhini in view of Shams.

In rejecting claims 14-17 under 35 U.S.C. §103(a), the Examiner relies primarily on Yakhini. However, as discussed in the section related to the first issue, Yakhini does not teach, mention, or even remotely suggest the currently claimed invention. Therefore, the 35 U.S.C. §103(a) rejection of claims 14-17 must certainly fail. Moreover, Shams does not teach, mention, or even remotely suggest that for which Shams in cited. Shams describes, in the cited passages in columns 2 and 10, user adjustment of a rectilinear grid superimposed on a microarray image. The passage has nothing whatsoever to do with classifying pixels as feature pixels or background pixels. There is not even the slightest suggestion of such classification in the passage.

6.   The rejection of claims 18 and 19 under 35 U.S.C. §103(a) as being unpatentable over Yakhini and Shams in further view of Bow.

In rejecting claims 18-19 under 35 U.S.C. §103(a), the Examiner relies primarily on Yakhini. However, as discussed in the section related to the first issue, Yakhini does not teach, mention, or even remotely suggest the currently claimed invention. Therefore, the 35 U.S.C. §103(a) rejection of claims 19-19 must certainly fail. As discussed above, Shams and Bow are entirely unrelated to the current application or claims.

7.   The rejection of claim 20 under 35 U.S.C. §103(a) as being unpatentable over Yakhini, Shams, , and Bow, in further view of Padilla.
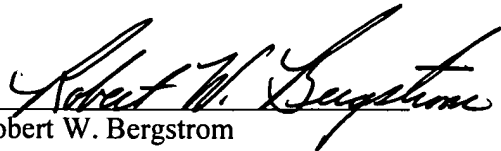
In rejecting claim 20 under 35 U.S.C. §103(a), the Examiner relies primarily on Yakhini. However, as discussed in the section related to the first issue, Yakhini does not teach, mention, or even remotely suggest the currently claimed invention. Therefore, the 35 U.S.C. §103(a) rejection of claim 20 must certainly fail. As discussed above, Shams, Padilla, and Bow are entirely unrelated to the current application or claims.

CONCLUSION

In summary, the reference Yakhini, used by the Examiner as the sole reference in the anticipation rejections and as the primary reference in the obviousness-type rejections, does not teach, mention, or suggest any method of classifying pixels within a region of interest of a microarray image in background pixels or feature pixels based on the intensities and locations of the pixels within the region by an iterative method. Yakhini is concerned with constructing and orienting a two-dimensional rectilinear grid partitioning a microarray image into cells, each rectangular cell containing a single feature. Yakhini does use various heuristics and assumed local background and feature regions within each cell based on the geometry of the cell, but uses these regions and assumptions only for finding the coordinates of the two-dimensional rectilinear grid, and not for classifying pixels within regions of interest as background or feature pixels. Moreover, Yakhini finds the two-dimensional grid for the entire microarray image based on collective evaluation of all of the cells, or features. There is no teaching, mention, or suggestion anywhere in Yakhini of computing an initial probability for a given pixel with regard to whether the pixel is a feature pixel or background pixel. There is no teaching, mention, or suggestion in Yakhini for iteratively computing probabilities, for each pixel within a region of interest, that the pixel is a feature pixel or background pixel iteratively. Yakhini is simply unrelated to the currently claimed invention.

Appellants respectfully submit that all statutory requirements are met and that the present application is allowable over all the references of record. Therefore, Appellants respectfully request that the present application be passed to issue.

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Respectfully submitted,
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CLAIMS APPENDIX

1. A method for classifying pixels of à microarray image with observed intensities within a region of interest, the method comprising:

    initially classifying pixels in the region of interest as either feature pixels or background pixels based on the intensities of the pixels; and

    iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels.

2. The method of claim 1 wherein a feature-pixel and background-pixel classification is stored in a feature mask.

3. The method of claim 2 wherein the feature mask includes binary values corresponding to pixels in the region of interest, a first binary value indicating that a corresponding pixel is a feature pixel and a second binary value indicating that a corresponding pixel is a background pixel.

4. The method of claim 1 wherein classifying pixels in the region of interest as either feature pixels or background pixels based on the observed intensities of the pixels further includes:

    determining a high pixel intensity and a low pixel intensity for the region of interest;

    determining an intermediate point between the high pixel intensity and a low pixel intensity;

    classifying pixels with observed pixel intensities greater than or equal to the intermediate point as feature pixels and classifying pixels with observed pixel intensities less than the intermediate point as background pixels; and

    iteratively reclassifying pixels based on an intermediate intensity between the mean intensity of feature pixels and the mean intensity of background pixels.

5. The method of claim 1 further including identifying hole pixels that are feature pixels surrounded by background pixels and background pixels surrounded by feature pixels and reclassifying hole pixels in order to increase continuity of feature-pixel and background-pixel

classification with respect to location within the region of interest.

6. The method of claim 1 wherein iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels further includes:

iteratively

computing intensity-based outlier feature-pixel statistics and outlier background-pixel statistics;

from the most recently computed intensity-based feature-pixel statistics and background-pixel statistics, determining, for each pixel, a Bayesian posterior probability P(F/i,x) that the pixel is a feature pixel and a Bayesian posterior probability P(B/i,x) that the pixel is a background pixel and classifying the pixel as a feature pixel when P(F/i,x) >= P(B/i,x);

until either a maximum number of iterations are performed or until fewer than a threshold number of pixels are reclassified from feature-pixel to background-pixel and from background-pixel to feature-pixel status in the most recently executed iteration.

7. The method of claim 6

wherein the Bayesian posterior probability P(F/i,x) is calculated as

$$P(F/i,x) = \frac{P(F,i,x)}{P(i,x)} = \frac{P(i/x,F)P(F,x)}{P(i,x)} = \frac{P(i/x,F)P(F/x)P(x)}{P(i,x)};$$

wherein the Bayesian posterior probability P(B/i,x) is calculated as

$$P(B/i,x) = \frac{P(B,i,x)}{P(i,x)} = \frac{P(i/x,B)P(B,x)}{P(i,x)} = \frac{P(i/x,B)P(B/x)P(x)}{P(i,x)};$$

and wherein a pixel is classified as a feature pixel when

$$\frac{P(F/i,x)}{P(B/i,x)} >= 1.$$

8. The method of claim 7 wherein Bayesian posterior probabilities P(F/i,x) and P(B/i,x) are calculated for each channel of a two-channel microarray, and a joint probability distribution function for two channels is then computed, which is then used for classifying pixels as feature pixels or background pixels.

9. A computer-readable medium encoded with computer-executable instructions that implement the method of claim 1.

10. Cancel

11. A computer-readable medium encoded with computer-executable instructions that implement a feature extraction program that includes a feature-location-and-size determination step that includes the method for classifying pixels with observed intensities within the region of interest of claim 1.

12-13. Cancel

14. A feature-extraction system comprising:

     a means for receiving and storing a scanned image of a microarray;

     a gridding means for determining putative feature positions and sizes within the scanned image of the microarray;

     feature-mask-generating logic that classifies pixels as feature-pixels and background-pixels based on pixel locations and intensities;

     preview-mode display logic that displays feature positions and sizes obtained from the generated feature mask, solicits feedback from a user, and corrects the feature positions and sizes; and

     a feature extraction module that extracts signal data from the scanned image of the microarray following user acceptance of initial feature locations and sizes displayed in preview mode.

15. The feature-extraction system of claim 14 wherein the feature-mask-generating logic classifies pixels as feature-pixels and background-pixels based on pixel locations and intensities by:

     initially classifying pixels in a region of interest as either feature pixels or background pixels based on the intensities of the pixels; and

     iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on

pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels.

16. The feature-extraction system of claim 15 wherein a feature-pixel and background-pixel classification is stored in a feature mask.

17. The feature-extraction system of claim 15 wherein classifying pixels in the region of interest as either feature pixels or background pixels based on the observed intensities of the pixels further includes:

determining a high pixel intensity and a low pixel intensity for the region of interest;

determining an intermediate point between the high pixel intensity and a low pixel intensity;

classifying pixels with observed pixel intensities greater than or equal to the intermediate point as feature pixels and classifying pixels with observed pixel intensities less than the intermediate point as background pixels; and

iteratively reclassifying pixels based on an intermediate intensity between the mean intensity of feature pixels and the mean intensity of background pixels.

18. The feature-extraction system of claim 15 wherein iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels further includes:

iteratively

computing intensity-based outlier feature-pixel statistics and outlier background-pixel statistics;

from the most recently computed intensity-based feature-pixel statistics and background-pixel statistics, determining, for each pixel, a Bayesian posterior probability $P(F/i,x)$ that the pixel is a feature pixel and a Bayesian posterior probability $P(B/i,x)$ that the pixel is a background pixel and classifying the pixel as a feature pixel when $P(F/i,x) >= P(B/i,x)$;

until either a maximum number of iterations are performed or until fewer than a threshold number of pixels are reclassified from feature-pixel to background-pixel and from

background-pixel to feature-pixel status in the most recently executed iteration.

19. The feature-extraction system of claim 18

wherein the Bayesian posterior probability P(F/i,x) is calculated as

$$P(F/i,x) = \frac{P(F,i,x)}{P(i,x)} = \frac{P(i/x,F)P(F,x)}{P(i,x)} = \frac{P(i/x,F)P(F/x)P(x)}{P(i,x)};$$

wherein the Bayesian posterior probability P(B/i,x) is calculated as

$$P(B/i,x) = \frac{P(B,i,x)}{P(i,x)} = \frac{P(i/x,B)P(B,x)}{P(i,x)} = \frac{P(i/x,B)P(B/x)P(x)}{P(i,x)};$$

and wherein a pixel is classified as a feature pixel when

$$\frac{P(F/i,x)}{P(B/i,x)} >= 1.$$

20. The feature-extraction system of claim 19 wherein Bayesian posterior probabilities P(F/i,x) and P(B/i,x) are calculated for each channel of a two-channel microarray, and a joint probability distribution function for two channels is then computed, which is then used for classifying pixels as feature pixels or background pixels.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.